malignant hyperthermia

Malignant hyperthermia is a severe reaction to particular drugs that are often used during surgery and other invasive procedures. Specifically, this reaction occurs in response to some anesthetic gases, which are used to block the sensation of pain, and with a muscle relaxant that is used to temporarily paralyze a person during a surgical procedure. If given these drugs, people at risk for malignant hyperthermia may experience muscle rigidity, breakdown of muscle fibers (rhabdomyolysis), a high fever, increased acid levels in the blood and other tissues (acidosis), and a rapid heart rate. Without prompt treatment, the complications of malignant hyperthermia can be life-threatening.

People at increased risk for this disorder are said to have malignant hyperthermia susceptibility. Affected individuals may never know they have the condition unless they undergo testing or have a severe reaction to anesthesia during a surgical procedure. While this condition often occurs in people without other serious medical problems, certain inherited muscle diseases (including central core disease and multiminicore disease) are associated with malignant hyperthermia susceptibility.

Frequency

Malignant hyperthermia occurs in 1 in 5,000 to 50,000 instances in which people are given anesthetic gases. Susceptibility to malignant hyperthermia is probably more frequent, because many people with an increased risk of this condition are never exposed to drugs that trigger a reaction.

Genetic Changes

Variations of the *CACNA1S* and *RYR1* genes increase the risk of developing malignant hyperthermia.

Researchers have described at least six forms of malignant hyperthermia susceptibility, which are caused by mutations in different genes. Mutations in the *RYR1* gene are responsible for a form of the condition known as MHS1. These mutations account for most cases of malignant hyperthermia susceptibility. Another form of the condition, MHS5, results from mutations in the *CACNA1S* gene. These mutations are less common, causing less than 1 percent of all cases of malignant hyperthermia susceptibility.

The *RYR1* and *CACNA1S* genes provide instructions for making proteins that play essential roles in muscles used for movement (skeletal muscles). For the body to move normally, these muscles must tense (contract) and relax in a coordinated way. Muscle contractions are triggered by the flow of certain charged atoms (ions) into muscle

cells. The proteins produced from the *RYR1* and *CACNA1S* genes are involved in the movement of calcium ions within muscle cells. In response to certain signals, the CACNA1S protein helps activate the RYR1 channel, which releases stored calcium ions within muscle cells. The resulting increase in calcium ion concentration inside muscle cells stimulates muscle fibers to contract.

Mutations in the *RYR1* or *CACNA1S* gene cause the RYR1 channel to open more easily and close more slowly in response to certain drugs. As a result, large amounts of calcium ions are released from storage within muscle cells. An overabundance of available calcium ions causes skeletal muscles to contract abnormally, which leads to muscle rigidity in people with malignant hyperthermia. An increase in calcium ion concentration within muscle cells also activates processes that generate heat (leading to increased body temperature) and produce excess acid (leading to acidosis).

The genetic causes of several other types of malignant hyperthermia (MHS2, MHS4, and MHS6) are still under study. A form of the condition known as MHS3 has been linked to the *CACNA2D1* gene. This gene provides instructions for making a protein that plays an essential role in activating the RYR1 channel to release calcium ions into muscle cells. Although this gene is thought to be related to malignant hyperthermia in a few families, no causative mutations have been identified.

Inheritance Pattern

Malignant hyperthermia susceptibility is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to increase the risk of a severe reaction to certain drugs used during surgery. In most cases, an affected person inherits the altered gene from a parent who is also at risk for the condition.

Other Names for This Condition

- anesthesia related hyperthermia
- Hyperpyrexia, Malignant
- Hyperthermia, Malignant
- Malignant Hyperpyrexia
- MHS - Malignant hyperthermia

Diagnosis & Management

These resources address the diagnosis or management of malignant hyperthermia:

- GeneReview: Malignant Hyperthermia Susceptibility
  https://www.ncbi.nlm.nih.gov/books/NBK1146
- Genetic Testing Registry: Malignant hyperthermia susceptibility type 2
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1835161/

- Genetic Testing Registry: Malignant hyperthermia susceptibility type 3
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C2930982/
- Genetic Testing Registry: Malignant hyperthermia susceptibility type 4
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1838102/
- Genetic Testing Registry: Malignant hyperthermia susceptibility type 5
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C2930984/
- Genetic Testing Registry: Malignant hyperthermia susceptibility type 6
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1866076/
- Genetic Testing Registry: Malignant hyperthermia, susceptibility to, 1
  https://www.ncbi.nlm.nih.gov/gtr/conditions/CN031421/
- MedlinePlus Encyclopedia: Malignant Hyperthermia
  https://medlineplus.gov/ency/article/001315.htm

These resources from MedlinePlus offer information about the diagnosis and management of various health conditions:

- Diagnostic Tests
  https://medlineplus.gov/diagnostictests.html
- Drug Therapy
  https://medlineplus.gov/drugtherapy.html
- Surgery and Rehabilitation
  https://medlineplus.gov/surgeryandrehabilitation.html
- Genetic Counseling
  https://medlineplus.gov/geneticcounseling.html
- Palliative Care
  https://medlineplus.gov/palliativecare.html

Additional Information & Resources

MedlinePlus

- Encyclopedia: Malignant Hyperthermia
  https://medlineplus.gov/ency/article/001315.htm
- Health Topic: Muscle Disorders
  https://medlineplus.gov/muscledisorders.html

Genetic and Rare Diseases Information Center

- King Denborough syndrome
  https://rarediseases.info.nih.gov/diseases/8433/king-denborough-syndrome
- Malignant hyperthermia
  https://rarediseases.info.nih.gov/diseases/6964/malignant-hyperthermia

Educational Resources

- Disease InfoSearch: Malignant hyperthermia
  http://www.diseaseinfosearch.org/Malignant+hyperthermia/4424
- JAMA Patient Page: Malignant Hyperthermia
  http://jamanetwork.com/journals/jama/fullarticle/201084
- MalaCards: malignant hyperthermia
  http://www.malacards.org/card/malignant_hyperthermia
- My46 Trait Profile
  https://www.my46.org/trait-document?trait=Malignant%20hyperthermia%20susceptibility&type=profile
- Orphanet: Malignant hyperthermia of anesthesia
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=423

Patient Support and Advocacy Resources

- Malignant Hyperthermia Association of the United States
  http://www.mhaus.org/
- National Organization for Rare Disorders (NORD)
  https://rarediseases.org/rare-diseases/malignant-hyperthermia/
- North American Malignant Hyperthermia Registry
  http://www.mhaus.org/registry/
- Resource List from the University of Kansas Medical Center
  http://www.kumc.edu/gec/support/malighyp.html

GeneReviews

- Malignant Hyperthermia Susceptibility
  https://www.ncbi.nlm.nih.gov/books/NBK1146

Genetic Testing Registry

- Malignant hyperthermia susceptibility type 2
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1835161/
- Malignant hyperthermia susceptibility type 3
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C2930982/
- Malignant hyperthermia susceptibility type 4
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1838102/
- Malignant hyperthermia susceptibility type 5
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C2930984/

- Malignant hyperthermia susceptibility type 6
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1866076/
- Malignant hyperthermia, susceptibility to, 1
  https://www.ncbi.nlm.nih.gov/gtr/conditions/CN031421/

ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22malignant+hyperthermia%22

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28Malignant+Hyperthermia%5BMAJR%5D%29+AND+%28malignant+hyperthermia%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D

OMIM

- MALIGNANT HYPERTHERMIA, SUSCEPTIBILITY TO, 1
  http://omim.org/entry/145600
- MALIGNANT HYPERTHERMIA, SUSCEPTIBILITY TO, 2
  http://omim.org/entry/154275
- MALIGNANT HYPERTHERMIA, SUSCEPTIBILITY TO, 3
  http://omim.org/entry/154276
- MALIGNANT HYPERTHERMIA, SUSCEPTIBILITY TO, 4
  http://omim.org/entry/600467
- MALIGNANT HYPERTHERMIA, SUSCEPTIBILITY TO, 5
  http://omim.org/entry/601887
- MALIGNANT HYPERTHERMIA, SUSCEPTIBILITY TO, 6
  http://omim.org/entry/601888

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